Abstract Submitted
for the MAR05 Meeting of
The American Physical Society

Density Functional Theory / Nudged Elastic Band Investigation of the Hydroxylation Reaction Mechanism Catalyzed by P450cam

MONTIAGO LABUTE, Theoretical Division, Los Alamos National Laboratory, GRAEME HENKELMAN, Department of Chemistry, University of Texas at Austin, BENJAMIN MCMAHON, Theoretical Division, Los Alamos National Laboratory —

We have calculated the complete minimum-energy reaction path for the hydroxylation of camphor by the P450 enzyme from Pseudomonas putida using the nudged elastic band method of Jonsson and co-workers[1]. Single-point force and energy calculations on pathway images were performed at the hybrid density functional level of theory (B3LYP) with large basis sets for the iron atom (6-311+G) and O_2 ligand (6-31+G*) on a 100 atom active site extracted from a recent high-resolution crystal structure[2]. Our model includes the heme group liganded to both Cys357 and dioxygen and we also include Thr251 and Asp252, which have been shown to significantly affect product yield by mutational studies[3]. We find that, upon transfer of the 2nd electron to the active site, the Fe-O_2 moiety is unstable and decays to a Fe-OOH- intermediate via a Asp252-H_2O proton transfer chain. The barrier for dioxygen cleavage and the identity of the reactive species will be discussed. [1] H. Jonsson, G. Mills, K.W. Jacobsen, in Classical and Quantum Dynamics in Condensed Phase Simulation, World Scientific (1998). [2] I. Schlichting, et al., Science 287, no. 5458, p. 1615-1622 (2000). [3] R. Davydov, et al., J. Am. Chem. Soc., 123: 1403-1415 (2001).

Montiago LaBute
Theoretical Division, Los Alamos National Laboratory

Date submitted: 01 Dec 2004

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